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MODEL-BASED ENGINEERING FOR PRODUCT-PROCESS DESIGN – DEALING WITH UNCERTAINTIES

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This paper provides a perspective on modelling and uncertainties in systematic model-based approaches in PSE for reliable and first-time right solution of product-process design related problems. Different challenges related to development and uses of systematic model-based approaches for product-process design are discussed and various sources of uncertainties in model-based approaches are highlighted. The significance of managing complexity including the uncertainties in model-based framework is highlighted and a hybrid systematic framework is proposed. The expected tasks from such a systematic framework thus becomes two-folds: (i) manage knowledge, data, models, associated methods, algorithms, tools integrated with work-flows/data-flows for specific product-process design problems, and (ii) manage uncertainties (of data, parameters, models, and their predictions) and their impact on decision-making related to specific product-process design problems. A model-based systematic framework for managing complexity and uncertainties in process design is given and discussed with respect to main ideas that need consideration. The application of the framework is highlighted with a product-process design from water industry while application of the framework on other product-process design problems can be found elsewhere. This perspectives paper is dedicated to Professor Sauro Pierucci for his contributions to CAPE and PSE.

1. INTRODUCTION

Process systems engineering (PSE) is concerned with understanding, analyzing and development of systematic procedures for the design, control, and operation of chemical process systems for manufacturing a wide range of products (Takamutsu, 1983). In parallel to a changing world, the domain of topics covered within chemical engineering are also changing and expanding, influencing thereby, the scope and significance of process systems engineering. As a result the scope of PSE has increased from the traditional areas of chemical engineering involving the oil, chemical and petrochemical industries to solving problems in emerging areas including life sciences (nutrients, health, medical sciences, biotechnology, biofuels), pharmaceutical industry, food industry, energy and enterprise-wide optimisation among others. (Grossman and Westerberg 2000; Grossman, 2005; Gani and Grossman, 2007; Gani, 2009). This expanding domain of applications for PSE naturally brings a new set of problems and challenges to work on, but at the same time ample opportunities to further advance the science of process systems engineering, that is, a systems approach to analyze, understand and solve problems effectively and innovatively.

2. MODELLING FOR PRODUCT-PROCESS DESIGN, COMPLEXITY AND UNCERTAINTIES

The problems related to product-process design differ in terms of the type of chemical(s) being produced. The products from traditional areas of chemical engineering such as petrochemical and chemical industries are usually commodity chemicals, small and/or structurally simple molecules, produced in large amounts and

typically driven my marginal profit. The main challenge here is optimization of the chemical process system to increase processing efficiency and reduce the production cost. On the other hand, the products in emerging areas especially in life sciences and pharmaceutical industries are usually large and/or complex molecules, produced in small amounts. Here, process optimization in terms of operational reliability, reproducibility (reduced product quality variability) and time of operation is usually the important driving factor for a candidate product-process. This means that although the principles of systems approach, that is, steps in the systematic solution of product-process design problems could be the same, the models and data, and the methods and tools needed in the various solution steps may be different.

That being said there are also common challenges in product and process development across the board of traditional and emerging areas of PSE as outlined in Table 1. Accordingly there is a constant drive for making new products through novel processing technologies for making novel products either to replace old/obsolete products from the market or meet new needs in the market. Next type of problem is about making new products from already existing processing capacity and installed technology in an attempt to diversify into new products for emerging needs in the market without the need for new capital investment. The third type of problem is about improving competitiveness (as marginal profit optimisation) through further optimising the efficiency and cost of production of the same product with new processing technologies perhaps through process intensification. This type of problems may also arise due to new regulatory changes, in which, for example, minimizing the CO₂ footprint of the production maybe imposed as well as other environmental regulation related to air and water pollution. The last type of problems relate to operation optimisation to maintain competitiveness in the market perhaps through continuous operation optimisation maybe by using advanced process control, offline versus online optimisation, model predictive controls.

Table 1 Different types of product-process design problems in traditional and emerging areas of PSE domain of applications

Problem type	Product	Process	Corporate purpose
Problem type#1	New	New	Make new products to replace old products or meet new market needs
Problem type#2	New	Old	Adapt to market needs to meet new demands or replace old products
Problem type#3	Old	New	Improve competitiveness through optimizing efficiency & cost /meet regulatory demands
Problem type#4	Old	Old	Maintain competitiveness through optimization of efficiency and cost

As pointed out by Gani (2009) modelling is a central element in model-based systematic solution of all product-process design problems classified in Table 1. These problems are solved by performing computer simulations of product-process candidates and evaluating their performances using systematic methods (algorithms) against specific objective functions (typically multi-criteria considered). This approach requires data and models to describe specific product-process combinations as illustrated in Figure 1. For example, models are needed to predict the behaviour of the product-process (quality of a product from a given a processing route, the efficient

of processing route and so on), to evaluate the performance of the product-process, to monitor and/or control the product-process, and many more (see Figure 1). These models may be of different type (different types of equations are used to represent the system); scales (may involve sub-systems requiring different size (molecular versus reactor scale) and time scales); complexity (number of equations, degree of non-linearity, dimension, *etc.*) and simulation mode (steady state, dynamic, batch, fed-batch, *etc.*).

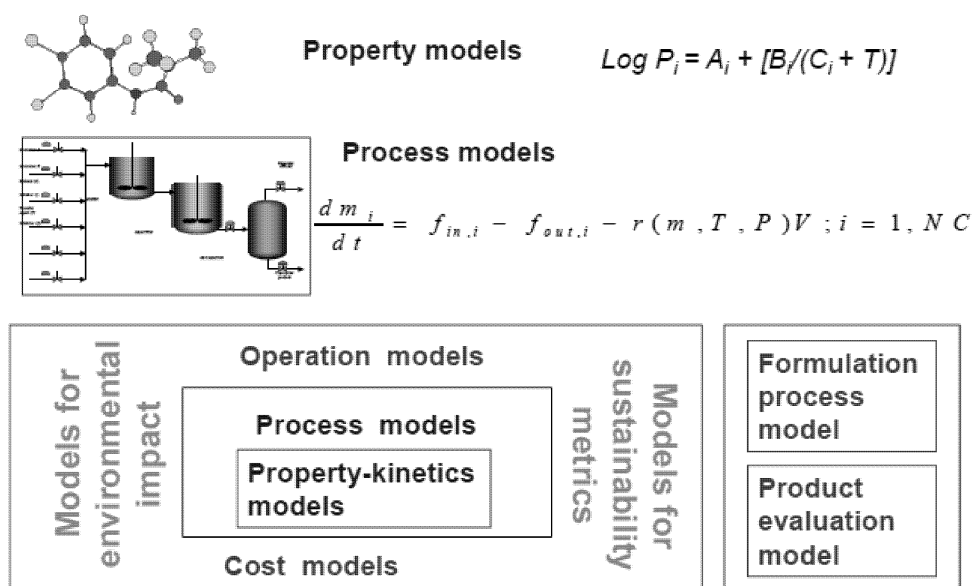


Figure 1 Evaluation of product-process candidates through models in model-based approach for product-process design

It is important to mention that this model-based approach is *not meant* to rid of experimentation in product-process development (which is *de-facto* the case in practice). Experimentation both at laboratory and pilot/demo scales shall remain important. However the model-based approach *do mean* to improve the product-process development by (i) reducing the number of experimentation needed (currently this is done based on experiences and expertise of the scientist and largely following a trial and error approach which is often costly with respect to time and resources), (ii) speeding up the development time for product-process as computer simulations for feasible product-process candidates can relatively be analyzed faster at different scales (for example, laboratory, pilot and demonstration scales) and (iii) screening and evaluating different process monitoring and control strategies in a fast and efficient way especially suitable for implementation of PAT in pharmaceutical manufacturing. While in Figure 1 the problem boundary is set to consider only product-processing technology interactions, modelling and PSE also provides the ability to develop and implement multi-criteria issues such as energy management, supply chain and sustainability within an enlarged system boundary for product-process design problems.

From the perspectives of developing and using model-based approaches for solution of product-process design problems, any systematic framework would need to handle the following issues:

- Product-process interactions occurring at multi-scale dimensions: important data related to the chemicals may come from different sources, at different scales of time and size; for example, the properties that define the product characteristics could be based on the microstructure of the molecule or material, while the process behaviour that needs to be monitored and controlled during operation

may be defined by the macroscopic (end-use) properties of the chemical system; the supply chain and sustainability issues need to be addressed at the mega-scale.

- Management of increasingly multidisciplinary information and knowledge: the conversion, for example, of the biomass feedstock through biocatalysis requires knowledge of organic synthesis, enzymes, reaction catalysis, bioreactor design and operation – information about these topics come from different disciplines namely biochemistry, protein-enzyme engineering, reaction and reactor engineering, process design and operation; sustainability analysis requires data, methods and tools from different disciplines from environmental sciences, chemical engineering sciences; the need for computer-aided methods for integration of methods and tools needed to solve the problems effectively; management of data, models and solution algorithm through for example databases requires knowledge from information technology.
- Management of uncertainties in data and models: As data, models and their parameters play a central role in computer simulations, predicting would-be product-process performances and related metrics from different candidates becomes very important to formally address and deal with uncertainties in various data, models and parameters used in the simulations (Sin *et al.*, 2009a). For example, parameters estimated for reaction rate constant, affinity constant and inhibition constant of a certain catalyst is almost often estimated from experimental data with measurement errors implying a certain error on the estimated parameters. The question then becomes what is the impact of these uncertainties on the model predictions, in other words, how reliable/representative and therefore meaningful are the computer simulations? Such uncertainties may be defined as technological risks, *i.e.*, failure of a selected product-process design to meet anticipated (or simulated) target efficiency/cost metrics. In addition to technological risks (this is expected to be low for traditional chemical engineering areas, but relatively higher for emerging chemical engineering areas, such as, life sciences where one is concerned with development of product-process design from scratch). Another source of uncertainties may also come from predicted market demand for the product in question which is a variable.

Referring to Table 1 there is a need to continuously keep improving product-process design (and development) by considering, for example, the demand for improved chemical-based products made from more sustainable raw material resources and employing more efficient processes to make them. Therefore, methods and tools suitable for current and future product-process design need to manage a collection of sub-problems that require effective, efficient and consistent handling of data and knowledge and uncertainties from different sources and at different time and size scales. This is inevitably a complex problem. Hence a systems approach that can efficiently “manage the complexity” is needed.

This contribution provides a perspective on the opportunities for the development and use of hybrid model-based frameworks for systematic solution of chemical product-process design problems with particular emphasize on dealing with uncertainties in data and models explicitly.

3. MANAGING COMPLEXITY THROUGH SYSTEMS APPROACH

A formal definition of the product-process design problem (Gani, 2004) is given by the following generic mathematical formulation:

$$F_{obj} = \{\mathbf{S}^T \mathbf{y} + f(\mathbf{x})\} \quad (1)$$

Subject to

$$\underline{D}_1 = \underline{h}_1(\mathbf{x}, \mathbf{z}, \mathbf{p}) \quad (2)$$

$$\underline{D}_2 = \underline{h}_2(\mathbf{x}, \mathbf{z}, \mathbf{p}) \quad (3)$$

$$0 \geq g_1(\underline{x}, \underline{z}, \underline{p}, \underline{\theta}) \quad (4)$$

$$0 \geq g_2(\underline{x}, \underline{z}, \underline{p}, \underline{\theta}) \quad (5)$$

$$B\underline{y} + C\underline{x} \leq \underline{d} \quad (6)$$

Where, the objective function, also called performance index, given in (Eq. 1) needs to be minimized or maximized and typically include multiple terms such as those related to product-process candidates but also processing efficiency, costs, sustainability and so on. The process model (Eq. 2) satisfies the conservation of mass and/or energy as a function of the product-process variables (\underline{x}), design variables (\underline{z}) and model parameters (\underline{p}). (the above generic formulation may also include a dynamic process model as inequality constraint when dealing with monitoring and control problems). The product performance model (Eq. 3) predicts the behaviour of the product during its application; the product-process structure equations (Eq. 6) generate the feasible product-process candidates (flowsheet structures) as a function of decision (integer) variables (\underline{y}) and \underline{x} ; and finally, the product-process constraints (Eqs. 4-5) define operational and/or chemical functional constraints ($\underline{\theta}$). Considering that the models maybe multi-scalar, non-linear and the variables involved may be integer as well as real, the generic problem defined above could represent a complex multi-dimensional problem of the MINLP type. Several variations of the above problem have also been formulated and solved in process optimization (Grossman, 2005), heat-mass exchange networks (Bagajewicz, 2000), and in product-process design (Karunanithi *et al.*, 2005; Conte *et al.*, 2011).

For successful solution of the above-formulated generic product-process design problem, one requires (i) product-process model objects for the chemical system in question, (ii) necessary data for design variables \underline{z} and model parameters \underline{p} for a wide range of models and systems, (iii) good initial estimate for \underline{x} and \underline{y} for different for the specific problem in question. One way to manage this complexity is to provide a hybrid model-based framework for handling a diverse set of design work-flows corresponding to a wide range of problems, through an integrated computer-aided system. Such systems need to have a knowledge base of data, a library of models, a collection of algorithms (the work-flow and data-flow guiding the engineer/scientist through the solution steps), and, other associated methods-tools (such as a tool to analyze data; a tool to create the missing model; a tool to screen feasible alternatives). Given that a successful solution is obtained from solution of above generic product-process design problem, an important question here is what are the role of uncertainties in data and models and how these can be formally addresses and dealt with?

4. MANAGEMENT OF COMPLEXITY PLUS UNCERTAINTIES

Within management of complexity, several model-based frameworks have been developed to address and systematically solve a number of product-process design related specific problems including:

- Model-based chemical formulation design (Conte *et al.*, 2011)

- Model-based process monitoring and analysis system (Singh *et al.*, 2009)
- Model based integrated process and controller design (Hamid *et al.*, 2010)
- Model-based sustainable process design (Carvalho *et al.*, 2009)
- Model-based process intensification (Lutze *et al.*, 2010)
- Model-based chemical product-process synthesis (d'Antoroaches and Gani, 2005)

In this paper we are highlighting only one of them, which address the uncertainty issue in model-based product-process design problems.

4.1. A framework

Uncertainty appears across a wide range of fields from physics to statistics, economics, environmental science (especially climate change), geophysical engineering (earthquake forecasting) and engineering, among others. What concerns engineering, **uncertainty** maybe defined as “the lack of certainty, a state of having limited knowledge about a system or process thereby unable to exactly define the future outcome as more than one outcome is possible”. Some possible outcomes of uncertainty may have undesired effects, *e.g.*, significant loss due to suboptimal engineering decisions (oversized reactor design, wrong choice of controllers, *etc.*) or large fluctuations in the product specs. Uncertainty and risk are two separate terms, but related in the following way: Those possible outcomes having undesired effects invokes the notion of **risk**. Hence dealing with uncertainty sets the stage for risk-based decision making in engineering works with potential cost-savings (Sin *et al.*, 2011).

Chemical engineers have faced and dealt with uncertainties from the very beginning of the profession. For example, uncertainties of certain aspects of engineering processes, lack of physical properties of chemicals; unpredictability of reaction rates particularly in the case of biotechnological processes; unpredictability of varying feedstock composition; variations in output demand, *etc.*, have forced design engineers to implement safety factors. Of course another effective method for dealing with uncertainties at production/operation scale is the use of plant wide control methods, which rejects disturbances and keep the plant operating at a defined trajectory. Both types of approaches have merits on their own when it comes to dealing with uncertainties, however they both have drawbacks too. For example, the choice of a safety factor for a equipment design (reactor, separator, heat-exchanger, pump, *etc.*) is arbitrary and varies widely among different industries (there is no quantitative guidance). Moreover, the magnitude of disturbances a plant-wide control scheme can reject will be determined by the choice of safety factor (hence design) as well as the selected components of the physical control system (*e.g.*, the pump capacity will have certain constraints with lower and upper bounds on the capacity).

Alternatively, one can use a proactive approach where sources of uncertainties are questioned and revealed systematically in product-process design problems (Sin *et al.*, 2009a). As regards sources of uncertainties, these may be grouped into three categories (i) input uncertainties – that reflects lack of knowledge about the model inputs (physical-chemical parameters) and data; (ii) structural uncertainty – that relates to the mathematical form of the model (note that models are approximations to systems rather than an exact copy); and (iii) stochastic uncertainty– this may be a component of the model itself (*e.g.*, a random failure events of pumps, *etc.*). The output is a reliability/robustness analysis of the model-based solution of the product-process candidate.

In this approach, one aims at a formal uncertainty analysis. In general, **uncertainty analysis** is concerned with propagation of the various sources of uncertainty (*e.g.*, data, parameters, kinetics, *etc.*) to the model output, *e.g.*, performance index). The uncertainty analysis leads to probability distributions of model predictions, which are then used to infer the mean, variance and percentiles of model predictions. *The sensitivity analysis*, on the other hand, aims at identifying and quantifying the individual contributions of the uncertain inputs to the output

uncertainty. Uncertainty and sensitivity analysis are usually (and preferably) performed in tandem with each other.

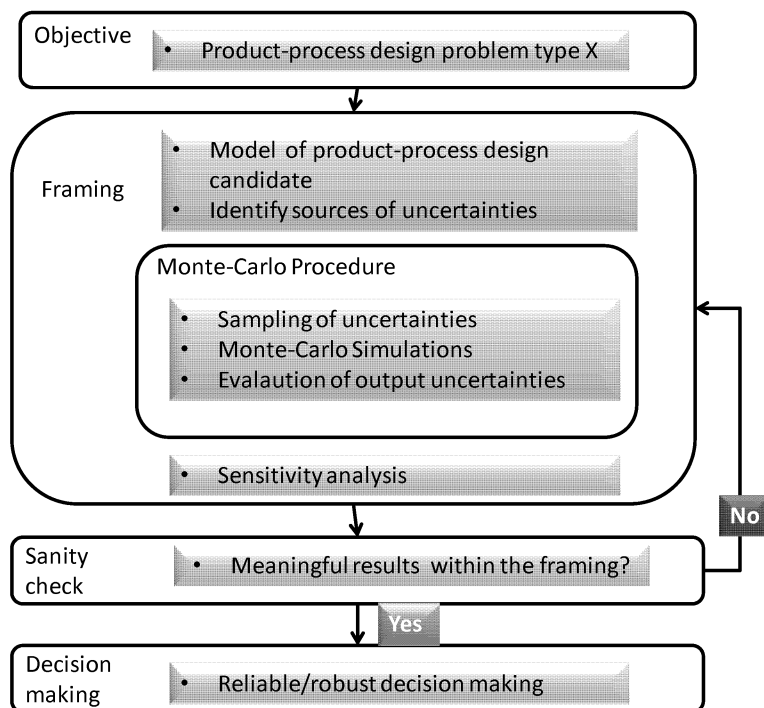


Figure 2 A systematic framework for managing uncertainties in model-based solution of product-process design problems

To answer the question posted earlier, what the impacts of uncertainties in data, models, parameters on the obtained solution of product-process design problems are, a systematic framework is proposed as highlighted in Figure 2. The first stage of the framework is setting the objective of the uncertainty analysis, e.g. what is the robustness of a given product-process design candidate. The second stage of the framework is called framing for uncertainty and sensitivity analysis. This stage deals with identification, understanding, calculating and analyzing uncertainties in the model predictions. This stage includes the following sub-steps: (i) model objects for product-process candidate, (ii) identification and characterisation of various sources of uncertainties, (iii) Monte-Carlo procedure to propagate different sources of uncertainties to the model predictions (Helton and Davis, 2003; Sin *et al.*, 2009b), which includes (a) sampling (e.g., using Latin-Hypercube Sampling), (b) Monte Carlo simulations and (c) evaluation of output (model predictions) uncertainties, (iv) sensitivity analysis (e.g., analysis of variance, standardized regression coefficients methods, etc) to find out which sources of uncertainties are important and by which fraction they contribute to uncertainties in the model predictions. Stage 3 is called sanity check, which scrutinizes the uncertainty/sensitivity results using product-process engineering expertise. This stage is merely to reflect on the framing scenario in which sensitivity and uncertainty analysis is carried out. If the results are deemed not meaningful from similar or previous experiences, e.g., the estimated uncertainties in the model predictions are unrealistically high, and then one has to go and debug or improve the framing scenario. If the results are deemed meaningful, then one can further go ahead and use them in decision making. In the last stage, the robustness of the model-based solution is evaluated by judging from a number of criteria including risk plots (e.g., probability of failure to meet target product constraints, such as 90% chance that the product purity constraints will be met).

The outcome of the framework of uncertainty analysis is the answer to the question of uncertainties the model-based solutions to product-process design problems. The answer could be in the following forms: answer 1) the model-based solutions to product-process design is reliable/robust hence go to implementation and experimentation step, answer 2) the model-based solution is very sensitive to a set of assumed data or model parameters. Hence further investigation is needed to zoom in on the data, parameters that needs accurate information before concluding on the reliability of the solution, answer 3) the given uncertainties in data and models are too large and hence one needs some experimental measurements (focused) to improve the accuracy of the data and models and re-use the systematic framework for model-based solutions.

4.2 Application of the framework

The framework has been applied to a number of problems related to process design and development from fermentation to water and biofuels areas (Sin *et al.*, 2009b;). The application related to product-process design problem from water industry is highlighted here, while the details of the can be obtained elsewhere (Sin *et al.*, 2009a; Sin *et al.*, 2011).

The purpose of the application of the uncertainty analysis framework was to answer the following question: given a process design candidate with its layout, operational configuration and feed profile, what are the uncertainties of the key process performance criteria? As the candidate process design flowsheet, BSM1 plant given in Figure 3 was considered in the analysis. Further details about the layout can be found in Sin *et al.*, 2009a.

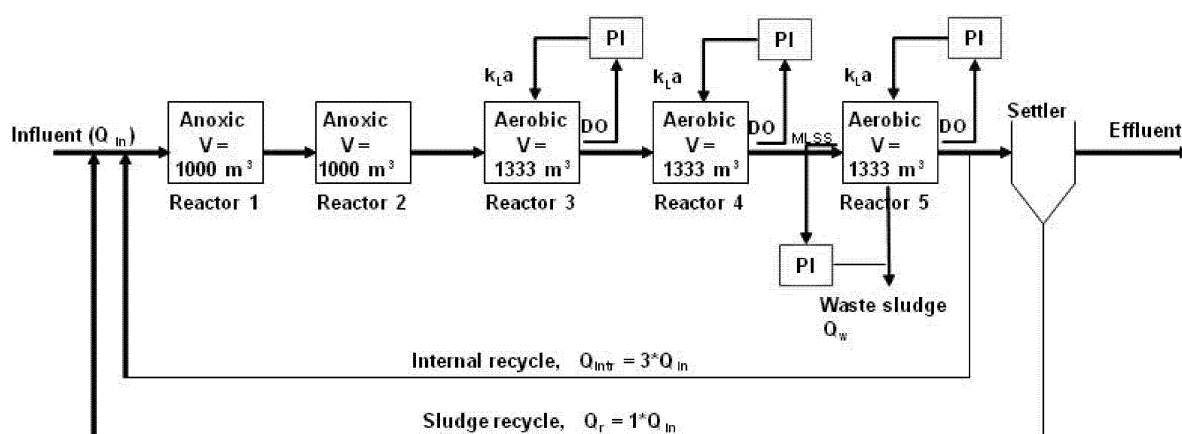


Figure 3 BSM1 process flowsheet considered as process design candidate in the uncertainty analysis framework (Sin *et al.*, 2009a)

In stage of the framework, the following sources of uncertainties were identified: the biokinetic model parameters, the performance of the aeration equipment and the hydraulic performance of the bioreactor while it was assumed that solid-liquid separation poses no additional uncertainty on the process performance. In total 26 parameters were identified as uncertain in the design and further they were assigned an uncertainty classes based on expert review (see Sin *et al.*, 2009a). Having identified and provided uncertainty ranges for each parameters, Monte Carlo simulations were then performed with the process model which quantified the uncertainties on the process performance criteria as mean with standard deviation as follows: effluent nitrogen concentration (12.9 ± 2.3 mg N/L of nitrate and 1.8 ± 0.9 mg N/L of ammonium), sludge production (2593 ± 384 kgSS/d) and electricity consumption (3660 ± 210 kWh/d). This candidate process design delivers a process performance with large

uncertainties especially with respect to effluent quality of the treated water –which is the product of this process. Further analysing the cumulative distribution function of the effluent quality of treated water, one finds that the probability of failure to meet the legal discharge limits is 0.75, which is unacceptably high. The sensitivity analysis found out that only 6 parameters out of 26 are mainly responsible for the uncertainties in the process performance. The most significant of them is found inert fraction of solids in the feed alone causing 50% of the uncertainty in the effluent nitrogen concentrations.

At stage 3 the results of uncertainty and sensitivity analysis were passed through a sanity check in which h process engineering expertise and past experiences were consulted, which confirm the validity of uncertainty and sensitivity analysis results. Hence the framework suggested improving the candidate process design by considering an additional unit operation such as grit removal aiming at decreasing the source of uncertainty in the feed. Another alternative was suggested to increase the safety factor (Sin *et al.*, 2011).

5. CONCLUSIONS

In this paper, a hybrid systematic model-based approach for solving product-process design problems has been discussed and an example of a systematic framework for dealing with uncertainties has been provided. The proposed framework falls under *management of complexity* where uncertainties inherently present in data and models are just another layer of complexity in the general or specific product-process design problems. An example of application of the framework has been highlighted for a process design problem from the water industry, which helped assess and improve the robustness of the candidate process design.

5. REFERENCES

- Bagajewicz M. J., 2000, A review of recent design procedures for water networks in refineries and process plants, *Computers and Chemical Engineering*, 24, 2113.
- Carvalho A., Matos HA., Gani R., 2009, Design of batch operations: Systematic methodology for generation and analysis of sustainable alternatives, *Computers and Chemical Engineering* 33, 2075-2090.
- Conte E., Gani R., Ng K. M., 2011, A systematic methodology for formulation design, *AIChE journal*, DOI 10.1002/aic.12458.
- D'Anterrosches L. and Gani R., 2005, Group contribution based process flowsheet synthesis, design and analysis. *Fluid Phase Equilibria*, 228-229, 141-146.
- Gani R., 2004, Chemical product design: Challenges and opportunities, *Computers and Chemical Engineering*, 28, 2441-2457.
- Gani R., 2009, Modelling for PSE and Product-Process Design, *Computer Aided Chemical Engineering*. 27, 7-12.
- Gani R. and Grossmann I. E., 2007, Process Systems Engineering and CAPE – What Next?, *Computer Aided Chemical Engineering*, 24, 1-5.
- Grossmann I. E., 2005, Enterprise-wide optimization: A new frontier in process systems engineering, *AIChE Journal*, 51, 1846-1857.
- Grossmann I. E., and Westerberg A. W., 2000, Research challenges in process systems engineering. *AIChE Journal*, 46, 1700–1703.
- Hamid M. K. A., Sin G., Gani R., 2010, Integration of process design and controller design for chemical processes using model-based methodology, *Computers and Chemical Engineering*, 34,683–699.
- Helton J.C. and Davis F.J., 2003, Latin hypercube sampling and the propagation of uncertainty in analyses of complex systems, *Reliability Engineering and System Safety*, 81, 23-69.

- Klatt K.-U. and Marquardt, W., 2009, Perspectives for process systems engineering – Personal views from academia and industry. *Computers and Chemical Engineering*, 33, 536-550.
- Karunanithi, A. T., Achenie, L. E. K. and Gani, R., 2005, A new decomposition based CAMD methodology for the design of optimal solvents and solvent mixtures, *Industrial and Engineering Chemistry Research*, 44, 4785-4797.
- Lutze P., Gani R., Woodley JM., 2010, Process intensification: A perspective on process synthesis, *Chemical Engineering and Processing: Process Intensification*, 49,547-558.
- Singh R., Gernaey K. V. and Gani R., 2009, Model-based computer-aided framework for design of process monitoring and analysis systems, *Computers and Chemical Engineering*, 33, 22-42.
- Sin G., Gernaey K.V., Neumann M.B., van Loosdrecht M.C.M and Gujer W., 2009a, Uncertainty analysis in WWTP model applications: a critical discussion using an example from design, *Water Research*, 43, 2894-2906.
- Sin G., Gernaey K.V., Neumann M.B., van Loosdrecht M.C.M and Gujer W.,2011, Global sensitivity analysis in WWTP model applications –prioritising sources of uncertainty, *Water Research*, 45,639-651.
- Sin G., Lantz A.E. and Gernaey K.V., 2009b, Good modelling practice (GMoP) for PAT applications: Propagation of input uncertainty and sensitivity analysis, *Biotechnology Progress*, 25,1043-1053.
- Takamatsu T., 1983, The nature and role of process systems engineering, *Computers and Chemical Engineering*, 7, 203-218.